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NOTICE.

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UNITED STATES.

HAFFKINE PROPHYLACTIC AND ANTIPEST SERUM.

THE HAFFKINE PROPHYLACTIC AGAINST PLAGUE AND A COMPARISON OF ITS ACTION WITH ANTIPLAGUE SERUM, BY P. A. SURG. H. D. GEDDINGS, U. S. M. H. S., ACTING DIRECTOR HYGIENIC LABORATORY.

The years 1893 and 1894 were characterized from an epidemiological point of view by the reappearance in several places, with a large number of cases, of the dreaded bubonic plague, which after a period of comparative quiescence and confinement to certain limited areas, again threatened to repeat its history of former outbreaks in former centuries. It seems undoubted that the starting points of the disease at this time were certain endemic foci of the disease in Thibet, Manchuria, and in other parts of China. It seems definitely known that the disease was brought from Longtcheu in 1893 and made its appearance the same year in Canton and Hongkong, thence being carried to British India and making its appearance in Bombay, Karachi, Poonah, and other ports. where it spread to an enormous extent and made ravages accompanied by a loss of life the total figures of which are simply appalling to contemplate.

It has long been a recognized fact that in grave cases of plague ordinary therapeutic measures are of little avail. The mortality has usually been from 85 to 95 per cent, and even with all the improvements of modern medical science this mortality has been but little reduced in recent epidemics. Naturally, therefore, the medical and scientific world hailed with joy any promises of a means more efficient than they had hitherto been in possession of for combating this terrible malady.

The announcement of Yersin and Kitasato, almost simultaneously,

of the discovery of the specific organism of the disease was followed closely by the announcement of Roux, Borrel, Calmette, and Yersin, of the production of a serum which it was claimed was both preventive and curative against plague. It was, indeed, a magnificent discovery; not made by accident, as have been many discoveries of scientific importance, but was the result of close reasoning, earnest work, and the most persevering research. But at the outset it was met by the formidable objection that for the preparation of this serum much time was necessary; the ordinary time required to immunize a horse up to a point that his serum would have preventive and curative action against plague varied from seven months to one year. It was also found that in many cases it was impossible to complete the immunization of the horse unless live culture of the plague bacillus was used in the process. It is needless to more than mention this to show the great danger that is attendant upon the production of the plague or antipest serum. In fact so great was the danger and so thoroughly was it recognized that up to within a few years Professor Roux, of the Pasteur Institute, had positively refused to undertake the immunization of 25 horses against plague at one and the same time.

Another point is that there sometimes comes a time in the preparation of a horse when increasing doses either of toxin or live culture will bring about the death of an animal upon which much time and labor has been expended. Therefore, Calmette, largely interested in this matter though he is from a scientific standpoint, has made the frank announcement that an objection to antipest serum is "the cost of producing the serum and the difficulty of obtaining it in sufficient quantity in order to vaccinate the entire population of a city or locality."

Therefore, with scarcely less enthusiasm was hailed the announcement of Haffkine of the production of a vaccinal fluid which would confer immunity against plague and which from the small cost and ease of its production would fill the the place of an agent for the protection of entire communities, cities, districts, or countries against an invasion of the malady.

Haffkine was not unknown to fame. A pupil and worker at the Pasteur Institute in Paris, he had made extensive investigation in India into the cause, method of spread, and method of prevention of another dreaded malady in that country, namely, Asiatic cholera, and had propounded the, at that time, startling theory that he was in possession of a fluid or vaccine which would prevent all cases of the disease. This announcement was the subject of bitter controversy—a controversy that endures to this day and it possibly may never be settled; but be that as it may, Haffkine practiced his inoculations against cholera in Spain during the years 1892, 1893, and 1894, and statistics would seem to bear out his claims to some extent.

Nevertheless the British Indian government, to whom it was a matter of vital importance to prevent in so far as possible the extension of plague over vast areas of country, densely populated, and with a population divided against itself by distinctions or differences in religion, laws of caste, etc., at once took up the matter, and Haffkine was authorized and invited to continue his experiments and make his inoculations under government aid and support.

Haffkine's original method.

The method of preparation as originally described by Haffkine was this: His bouillon for growing the organism was prepared from goat's

flesh, which was macerated with dilute hydrochloric acid, presumably for the purpose of converting some of the albumen into peptone. This bouillon was then transferred to large flasks which were inoculated with the *bacillus pestis*, and to the bouillon at this time was added a certain portion of "gee" or native butter. This was, of course, to some extent emulsified, but the larger portion floated on the surface of the liquid and formed an oily layer, the result of which was that the organism was grown under practically anærobic conditions. In about three weeks the entire fluid was subjected to a temperature of about 70° C., and a small proportion of some germicidal agent having been added to preserve it, the fluid was ready for use.

Let us here for a moment review the results of the method of growth. No mention is made that the culture with which the bouillon was inoculated was of any special degree of virulence. It was usually obtained, it is said, direct from the bodies of those dead of the disease, which would insure undoubtedly a certain degree of virulence but not by any means the most exalted. The presence of the oil or fat in a layer upon the surface of the bouillon, thus growing the organism under anærobic conditions, is not calculated to increase or preserve the highest degree of virulence. Therefore, it is thought only fair to assume that the cultures as used by Haffkine prior to being killed by heat were not as virulent cultures as could be obtained by other methods. Reference to literature will show that Haffkine recommends doses of his prophylactic of from 2 c. c. to 5 c. c., which, considering the toxicity of the plague organism, might seem a large dose.

Modification of Haffkine's original methods.

In taking up the subject of the manufacture of Haffkine prophylactic or vaccinal fluid, the Pasteur Institute recommended a modification of Haffkine's original method. It was suggested that ordinary agar-agar (peptonized to the extent of 1 per cent) should be spread over large surfaces and these surfaces then heavily inoculated with a suspension of an agar culture of the bacillus pestis rendered as virulent as possible by special methods of cultivation. This resulted in a very heavy growth upon the agar plates which were allowed to grow at a temperature of 37° C. for four days, when the growth was removed by being washed or agitated with 100 c. c. of peptone free bouillon to each flask or plate. This suspension of the virulent culture of the bacillus pestis was then killed by subjection to a temperature of 70° C. for two or three hours, and the liquid, turbid in character and containing a mass of the dead microbial bodies was then immediately bottled or placed in tubes without the addition of any germicidal agent, and in the case of tubes these were sealed in the flame, or in the case of bottles they were stoppered under aseptic precautions. The non addition of germicidal agent is simply carrying out the general theory and practice of the Pasteur Institute in the preparation of all sera and fluids.

This method was communicated to this laboratory by Surgeon Wasdin, U. S. M. H. S., who was at the time studying at the Pasteur Institute at Paris. The method was given a very full trial in this laboratory, and the resulting liquid was one whose appearance and general characteristics were in the highest degree satisfactory. But it was found that the chances for extrinsic contamination were too numerous in the various manipulations which had to be carried out, and that frequently large numbers of culture flasks or plates were contaminated and rendered useless by the growth of molds or ordinary air organisms, especially

the hay bacillus, whose spores are notably so resistant to the ordinary germicidal measures. After a full trial, therefore, and the preparation of a considerable quantity of the prophylactic by this method, it was abandoned, and the plan was inaugurated of simply growing virulent cultures of the bacillus pestis in ordinary bouillon, peptonized, in flasks or vessels which exposed a large surface to the air. Fernbach flasks or Erlenmeyer flasks, of large capacity and only partially filled, were used for this purpose. No difficulty was experienced under this method in securing abundant successive crops of the organism perfectly characteristic in all respects and possessing a high degree of virulence.

The cultures were allowed to grow, as a rule, from twenty-one to twenty-eight days and were then killed by exposure, for two hours, to a carefully regulated temperature of 70° C. Each lot of prophylactic as finished was tested culturally to be sure that all plague organisms had been killed, and the earlier lots manufactured were tested on rabbits and other laboratory animals for innocuousness and several lots were tested on similar animals for efficiency. In this way large quantities of fluid have been made and distributed to the various quarantine officers, national, State, and local, of the United States, and a certain quantity of it was used in the outbreak of plague in Honolulu and, more recently, in the inoculation of about 600 persons in San Francisco, Cal.

In all, in the neighborhood of 400,000 doses of 1 c. c. each have been manufactured and either distributed or are on hand at this time. This dose was determined upon as the standard in preference to the larger doses of Haffkine in view of the known potency and toxicity of the cultures employed in the manufacture.

Results from use of the Haffkine.

Let us now inquire into the results which have been obtained by the use of the Haffkine prophylactic. We are fortunately in possession of figures which seem to triumphantly vindicate the value of the procedure.

In the Bombay Presidency in British India it is noted in a series of observations as follows:

	Number.	Cases.	Deaths.
Inoculated	147	2	0
Noninoculated	172	12	6
Inoculated	147	3	0
Noninoculated	127	10	6
Inoculated	71	8	3
Noninoculated	64	27	26

These figures show that in addition to affording a very large proportion of protection against the disease the mortality was reduced by 80 or 90 per cent. An instance of the average mortality is afforded by the statistics showing that in the city of Hubli the mortality among those not inoculated reached the appalling figure of 657 per 1,000 of those attacked. Further, in the cities of Bombay and Moffusil the following figures are given:

	Inoculated.	Cases.	Deaths.
Bombay	8,200	18	2
Moffusil	429	7	0
Noninoculated		26	24

The duration of the immunity conferred was stated to be several months and this immunity was much increased by a second or even by a third inoculation.

In Lanowlie, India, among 323 inoculated people there were only 14 attacks and 7 deaths. In the same city among 377 not inoculated 78 were attacked, with 58 deaths. Of the Mussulman population of Bombay, 5,184 were inoculated. Of these 7 died. Among 8,146 not inoculated 177 died. (*a*)

The medical society of Bombay in November last discussed at one of their sessions the propriety and value of Haffkine inoculation. By some it was considered dangerous to introduce into the human economy a liquid containing plague bacilli, and they expressed some fear that these bacilli may not have been all killed by heat and might produce an attack of the disease. There were only 4 votes in the whole assembly that appeared to indorse this position. The meeting by an overwhelming majority agreed that Haffkine's prophylactic conferred immunity and that this was prolonged for six months after the inoculation, and that the immunity was considerably strengthened by a second inoculation within ten days after the first.

In support of this position they adduced the following statistics of the inoculations performed at Sharwar:

Inoculated once	5,712
Attacks	69
Deaths	31
Inoculated twice	3,349
Attacks	9
Deaths	5
Not inoculated	5,614
Attacks	957
Deaths	756

Action and limitation of use of the Haff kine.

The inoculation by Haffkine prophylactic causes a mild intoxication by the products of the plague bacillus. In about six hours the patient suffers from some malaise, headache, depression, and sometimes slight fever, which continues may be two days. The site of the inoculation is congested and there is local swelling and tenderness, which disappear. An eruption sometimes occurs. The symptoms appear never to have been so intense that infants suckled by nurses who had been inoculated suffered any inconvenience, nor was there any disturbance of the normal course of pregnancy among pregnant women who were inoculated.

A point which must not be lost sight of is one to which particular attention was drawn by Calmette and Salembini in their report on the outbreak of the plague at Oporto, viz, that should a person who has already been exposed to plague, and in whom the infection is in the incubative stage, be inoculated with Haffkine prophylactic, the administration of the prophylactic would probably hasten the appearance of the disease and be conducive to a fatal result. This is not difficult to comprehend, for death from plague is a result not only of the septicæmia, but of a profound toxæmia.

The toxin contained in the Haffkine prophylactic added to that which is generated during the course of the disease would bring about an overwhelming effect and the patient would probably succumb. There-

a Montenegro, "Bubonic plague," p. 71, *et seq.*

fore, the use of Haffkine prophylactic should be limited to those who have not as yet been exposed to direct infection, but who may subsequently be exposed owing to the presence of the disease in the town or community in which they dwell. Too much stress can not be laid upon this point, as a result of inoculation where exposure to infection, or actual infection, has already occurred would not only lead to disappointment, but probably to disaster.

Relative value of the Yersin antipest serum and the Haffkine prohphylactic.

This brings up the question of the relative value of the Yersin, or antiplague serum, of which mention has previously been made, and the Haffkine prophylactic. The two substances act in an entirely different way and fill entirely different roles. As has just been said, the use of Haffkine prophylactic among those actually exposed to infection or already infected is a source of added danger. To this objection the antiplague serum is *not* liable, as it is not only preventive in action, but is also the *only known efficacious remedy for the cure of the malady.*

This article possibly can not be brought to a better close than by stating *in extenso* the masterly exposition which Calmette has recently made of the advantages and disadvantages of the two agents in his address before the International Congress of Hygiene and Demography at Paris, which has only recently adjourned.

The advantages of the antiplague serum are—

"First. It confers immunity almost absolute and immediate.

"Second. The injection of the serum is not painful and is therefore readily accepted, even by children.

"Third. It is never harmful.

"Fourth. The serum, when prepared antiseptically, is a product whose activity remains intact a very long time, in fact almost indefinitely."

The disadvantages are—

"First. The very short duration of the immunity.

"Second. The cost of producing the serum and the difficulty of obtaining it in sufficient quantity in order to vaccinate the population of an entire city, which should be done at intervals of fourteen days.

"Third. The difficulty of making obligatory, or even of inducing a majority of the population to accept a vaccination which must be repeated so frequently."

These objections, let it be distinctly understood, do not militate to the slightest extent against the value of the serum as a curative agent, but simply against its practical use as a prophylactic.

It has distinct uses under the following suggested conditions:

"(*a*) On board of infected vessels during the voyage to prevent the disease spreading among the passengers and crew.

"(*b*) In order to immunize the personnel of those employed in the lazarettoes or detention hospitals as well as those concerned in the unloading or disinfection of merchandise brought by suspected vessels or vessels having had actual cases of plague on board.

"(*c*) On the docks or in the warehouses and stores by those engaged in handling suspected or infected merchandise.

"(*d*) And most important of all in times of epidemic for the immediate protection of persons found in contact with the sick or who may be already infected."

Recurring again to the Haffkine prophylactic, Calmette continues:

"That the vaccination with Haffkine prophylactic is very useful in infected countries for the following reasons:

"First. That large quantities of Haffkine vaccine may be readily

prepared almost without cost and in a very short time by growing cultures of the bacillus of plague for one month and heating them at 70° C.

"Second. Inoculation by the Haffkine prophylactic can usually be made acceptable without much difficulty as it produces only a little inflammation and swelling about the immediate site of the inoculation.

"Third. The entire population of a village, city, or country may be inoculated with the prophylactic and susceptibility to the disease limited or eliminated, and as a consequence its spread prevented."

It is open to some objections, however, which he states as follows:

"(*a*) The danger of inoculation to those who have already been exposed to or have contracted the infection."

This has been fully dwelt on, and deductions may be drawn from the statements already made.

"(*b*) Injection of the prophylactic sometimes produces considerable reaction. It is usually slight, but may sometimes be sufficiently great to oblige those inoculated to take to their beds."

(*c*) He maintains that "the prophylactic retains its activity for a period not greater than six months, the combined action of air and light very quickly attenuating the toxicity of the fluid." This might be avoided by keeping the fluid in the dark in a cool place or in bottles or containers entirely filled and carefully sealed. In this way there can be no exposure to the air.

With this brief résumé of the advantages and disadvantages both of the serum and the prophylactic it is thought that this article can appropriately be brought to a close.

There is no infallible remedy against plague. The antiplague serum is largely effectual and has much diminished the mortality among those treated by it. The serum also possesses valuable prophylactic qualities as detailed above. In the Haffkine prophylactic we have an agent which is readily producible in large quantities, is free from danger when used under proper precautions and with which it is feasible to confer an effectual immunity against plague in whole villages, cities, or districts. Taken in connection with reasonably enlightened sanitary precautions, thorough disinfection, and those measures which have proven of so much value in other contagious or infectious diseases, we may say with certainty or affirm with confidence that in the antiplague serum and in the Haffkine prophylactic we have remedies with which we can successfully combat a disease which in former times has baffled all human skill.

Shipment of figs and raisins from Smyrna prohibited during prevalence of plague and for a period of sixty days after its cessation.

In response to inquiries from importers the Secretary of the Treasury has sent the following dispatch relating to the embargo on figs and raisins from Smyrna as set forth in his letter to the Secretary of State and published in the PUBLIC HEALTH REPORTS, August 10, 1900, page 1977:

"TREASURY DEPARTMENT, *August 25, 1900.*

"Paragraphs 4 and 12, Article IV, Quarantine Regulations to be observed at foreign ports and at sea, prohibit shipment of figs and raisins from Smyrna. These regulations will be waived after Smyrna has been officially declared free from bubonic plague for sixty days.

"O. L. SPAULDING,
Acting Secretary."

Summary of the plague situation in San Francisco up to and including August 18.

On June 14 Surg. J. J. Kinyoun reported that there had been, from March 7 to June 2, inclusive, in San Francisco, 11 deaths from plague, in 10 of which the diagnosis was confirmed by bacteriological investigation. There were at that time 3 cases suspected of plague under investigation, 1 of which he was positive was genuine and which bacteriological investigation, concluded on June 22, proved to be genuine.

On July 7 another fatal case was reported as having been admitted to the city hospital under diagnosis of typhoid fever, cultures from this case having been made by the local board of health of San Francisco, the State board of health of California, and the quarantine officer of Victoria, British Columbia.

On August 12 another case of plague resulting fatally was reported from the city hospital, San Francisco; this case like the others being a resident of Chinatown.

On August 18 1 more case was discovered in which the microscopical examination gave confirmatory results.

By this summary it may be seen that there were 9 cases in the months of March, April, and May, 4 cases in June, 1 in July, and 2 in August; 16 cases in all.

[Reports to the Surgeon-General United States Marine-Hospital Service.]

Prevailing diseases at Cape Nome, Alaska.

NOME, ALASKA, *August 4, 1900.*

SIR: I have the honor to inform you that there are now at the detention hospital 7 cases of smallpox. Six of these are convalescent. The seventh is a new case, a soldier from the barracks, admitted August 2. The physician in charge at the hospital states that this case is one of very mild form.

Dr. Hornsby, one of Lieutenant Jarvis's appointees, completed during the week just ended a second house-to-house and tent-to-tent inspection of the town and vicinity and reports that he found no cases of smallpox or typhoid fever, about 12 cases of measles, 15 to 18 cases of pneumonia, and a great many cases of tonsilitis.

Respectfully,

BAYLIS H. EARLE,
Assistant Surgeon, U. S. M. H. S.

Smallpox at Cape Nome.

[Telegram.]

SEATTLE, WASH., *August 23, 1900.*

At Dutch Harbor. Transport Seward arrived from Nome. Twenty-three cases of smallpox from beginning of outbreak until August 8. One varioloid removed from army camp at Nome August 8. Informant the army surgeon in charge of Post Nome. Expect to arrive Nome August 17.

LLOYD,
Dutch Harbor, Alaska.